isolated using *aro*A DNA from other bacteria as hybridization probes. The sequence of the *P. haemolytica aro*A gene is shown in SEQ ID NO. 1. Similarly other genes can be isolated from *P. haemolytica*. Another desirable gene for mutations is the *Pha*I endonuclease gene, which is provided in *Pha*I Mtase (ATCC Accession No. ATCC 69500). Other genes in which mutations may be desirable are genes in the leukotoxin operon (C, A, B, D) and neuraminidase.

Claim 34 has also been amended to recite an isolated *P. haemolytica* bacterium. Support for the amendment can be found in the specification at, *inter alia*, page 4, lines 11-13. "In yet another embodiment of the invention an isolated and purified *P. haemolytica* strain is provided."

The Rejection of Claims 34-37 Under the Doctrine of Double Patenting

Claims 34-37 have been rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-4 of U.S. Patent No. 5,849,305. Applicants will refrain from filing an appropriate terminal disclaimer until receipt of an indication of allowability of the claims.

The Rejection of Claims 34-37 Under 35 U.S.C. §112, second paragraph

Claims 34-37 stand rejected under 35 U.S.C. §112, second paragraph as indefinite. Claims 36 and 37 have been canceled. Therefore, the rejection is moot as it applies to claims 36 and 37. Applicants respectfully request reconsideration of the patentability of claims 34 and 35.

The Office Action requests that the phrase *P. haemolytica* be spelled out. Claim 34 has been amended to spell out *Pasteurella haemolytica*.

The Office Action asserts that the claims do not recite an isolated or purified composition and therefore the claims recite a product of nature. Claim 34 has been amended to recite an isolated *P. haemolytica* bacterium. Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 34-37 Under 35 U.S.C. §112, first paragraph

Claims 34-37 stand rejected under 35 U.S.C. §112, first paragraph as not enabled for their full scope. Claims 36 and 37 have been canceled, therefore the rejection is moot as to these claims. Applicants respectfully request reconsideration of claims 34 and 35.

The Office Action asserts that the specification is enabled only for claims limited to site directed mutations of *P. haemolytica* using *aro*A, *Pha*I, leukotoxin operon (C, A, B, D) and neuraminidase genes. In order to advance prosecution claim 34 has been amended to recite that the mutation occurs in a gene selected from the group consisting of *aro*A, *Pha*I, leukotoxin C, leukotoxin A, leukotoxin B, leukotoxin D, and neuraminidase. As the Office Action recognizes, the specification teaches the site directed mutagenesis of *P. haemolytica aro*A, *Pha*I, leukotoxin C, leukotoxin A, leukotoxin B, leukotoxin D, and neuraminidase genes. See specification, page 7, lines 4-12.

Moreover, the claim has been amended to clarify that the DNA which is introduced both contains the mutation and is methylated by an enzyme having the same sequence specificity as *Pha*I. Thus, it is now clear that it is not the mutation which is methylated but the DNA which is introduced which is methylated.

In addition, the claim amendment clarifies that not any DNA region can be introduced, but only DNA which comprises all or part of the recited gene which contains the mutation. It is believed that the claim clarifications address the issues raised regarding use of any region of the genome and regarding any mutation being methylated. Applicants respectfully request withdrawal of the rejection in view of the amendments.

The Rejection of Claims 34, 36, and 37 Under 35 U.S.C. §112, first paragraph.

Claims 34, 36, and 37 stand rejected under 35 U.S.C. §112, first paragraph as not enabled for their full scope. Claims 36 and 37 have been canceled. Therefore, this rejection is moot as

applied to these claims. Applicants respectfully request reconsideration of the patentability of claim 34.

The Office Action asserts that the claims are not enabled for vaccines comprising the viral vectors for any antigen. Claim 34, as amended, does not recite vaccines comprising viral vectors for any antigen nor does it implicate a gene therapy approach. Claim 34 recites a vaccine comprising a bacterium. Although Applicants do not wish to be bound by any theory of operation or mechanism, it is believed that the bacteria in the vaccine function as standard immunogens, and not by transfer of their genetic material to the vaccinated animal for expression by the animal. No such mechanism is believed to be involved.

Applicants respectfully request reconsideration of the patentability of claim 34.

The Rejection of Claims 34, 36, and 37 Under 35 U.S.C. §112, first paragraph

Claims 34, 36, and 37 stand rejected under 35 U.S.C. §112, first paragraph as not enabled for their full scope. Claims 36 and 37 have been canceled. Therefore, this rejection is moot as applied to these claims. Applicants respectfully request reconsideration of the patentability of claim 34.

The Office Action asserts that the claims are not enabled for the induction of protective immunity to such organisms as *Staphylococcus epidermidis* or AIDS virus. Claim 34 has been amended to recite a vaccine for inducing protective immunity against *P. haemolytica*. Claim 34 does not recite induction of protection against infections other than *P. haemolytica*. Claim 34 is therefore fully enabled by the specification. Applicants respectfully request reconsideration of claim 34.

The Rejection of Claims 34-37 Under 35 U.S.C. §103(a)

Claims 34-37 stand rejected under 35 U.S.C. §103(a) as unpatentable over Homchampa

et al. Claims 36 and 37 have been canceled. Therefore, this rejection is moot as applied to these claims. Applicants respectfully request reconsideration of the patentability of claims 34 and 35.

Claims 34 and 35 are drawn to vaccines comprising an isolated *P. haemolytica* bacterium which comprises a mutation in a gene selected from the group consisting of *aro*A, *Pha*I, leukotoxin C, leukotoxin A, leukotoxin B, leukotoxin D, and neuraminidase. The Office Action asserts that the claims are obvious over the teachings of Homchampa. Homchampa is cited as teaching the insertion of a kanamycin-resistance gene into the *aro*A gene of *P. multocida* resulting in inactivation of the *aro*A gene. Homchampa, however, does not teach or suggest the introduction of mutations into bacteria of the type claimed, namely *P. haemolytica.*

The *P. multocida* taught by Homchampa is not of the same species of bacteria as *P. haemolytica*, as asserted in the Office Action. These two species, *multocida* and *haemolytica*, were formerly classified as members of the same genus (*Pasteurella).* However, these two species are so distant genetically that they have been reclassified as members of different genera! *P. haemolytica* as taught in the present invention has been reclassified and renamed as *Mannheimia haemolytica*. This reclassification is based on the extreme distinctness of DNA, and in particular 16S rRNA. See Angen *et al.* Investigations on the species specificity of Mannheimia (Pasteurella) haemolytica serotyping. Vet. Microbiol. 65:283-290. 1999; Angen *et al.* Taxonomic relationships of the (Pasteurella) haemolytica complex as evaluated by DNA-DNA hybridizations and 16S rRNA sequencing with proposal of Mannheimia haemolytica gen. nov., comb. nov., Mannheimia granulomatis comb. nov., Mannheimia glucosida sp. nov., Mannheimia ruminalis sp. nov. and Mannheimia varigena sp. nov. Int. J. Syst. Bacteriol. 49 Pt 1:67-86. 1999. Thus, given the divergence of these two species, one of ordinary skill in the art would not have reasonably expected that Homchampa's results with *P. multocida* would imply

success for the claimed *P. haemolytica*, now *Mannheimia haemolytica*. Applicants respectfully request withdrawal of the rejection.

Applicants respectfully request the withdrawal of all rejections and the allowance of all pending claims.

Respectfully submitted,

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